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03-1237

IN THE

Supreme Court of the United States

MERCK KGaA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD.;
THE BURNHAM INSTITUTE

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMICUS CURIAE BRIEF OF THE AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF NEITHER PARTY

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AMICUS CURIAE BRIEF OF THE AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF NEITHER PARTY

The American Intellectual Property Law Association ("AIPLA") respectfully submits this brief as *amicus curiae* in support of neither party.

INTEREST OF THE *AMICUS CURIAE*

AIPLA is a national bar association of more than 16,000 members with interests and practices primarily in the areas of patent, trade secret, trademark, copyright, and other aspects of intellectual property law.[1] Unlike areas of practice in which separate and distinct plaintiffs' and defendants' bars exist, most intellectual property law attorneys represent both intellectual property owners and alleged infringers.[2]

AIPLA has no interest in any party to this litigation or any stake in the outcome in this case, other than its interest in helping to ensure a correct interpretation of the § 271(e)(1) safe harbor. In accordance with Supreme Court Rule 37.3(a), AIPLA has obtained written consent to the filing of this brief from the counsel of record for both parties. The letters of consent have been filed with the Clerk of the Court.

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[1] In accordance with Supreme Court Rule 37.6, *amicus curiae* states that this brief was not authored, in whole or in part, by counsel to any party, and no monetary contribution to its preparation or submission was made by any person or entity other than the *amicus curiae* and its counsel.

[2] AIPLA has been asked to inform the Court that the Federal Circuit Bar Association, an organization of approximately 2,900 attorneys whose practices involve the U.S. Court of Appeals for the Federal Circuit, also affirmatively supports the positions taken in this brief.

SUMMARY OF ARGUMENT

The statutory safe harbor of 35 U.S.C. § 271(e)(1) shelters activity from patent infringement liability if it is "solely for uses reasonably related to the development and submission of information" to the United States Food and Drug Administration (FDA). The FDA requires that applicants seeking regulatory approval of new drugs support their applications with data and information from a broad range of preclinical and clinical studies.

A panel of the Federal Circuit in this case advanced a narrow interpretation of § 271(e)(1) that appears to limit the safe harbor protection to clinical studies using human subjects while excluding many other types of studies typically included in applications for FDA approval, including preclinical *in vitro* and animal studies, comparative studies, and safety profiling studies. The excluded studies, however, are embraced by the plain language of the statute. Because the panel applied an erroneous legal standard, the decision below must be vacated and remanded.

A remand of this case does not mean that all drug discovery activity, especially at the earliest stages, qualifies for protection under § 271(e)(1). Early drug discovery activity may aim merely to identify promising compounds for further study, not to evaluate their safety or effectiveness for FDA regulatory purposes. This Court should not adopt an interpretation that extends the safe harbor to cover all such early drug discovery activity, which would deviate from the statutory language.

Finally, although the dissenting opinion in the Federal Circuit focused largely on the applicability of a common-law experimental use exception to infringement liability, the Court need not and should not reach this distinct and tangential issue in interpreting § 271(e)(1).

ARGUMENT

I. THE FEDERAL CIRCUIT PANEL OVERLOOKED IMPORTANT ELEMENTS OF THE FDA REGULATORY PROCESS.

By its plain language, the statute at the center of this controversy invokes the federal regulatory process through which the FDA approves the sale of pharmaceutical drugs and medical devices:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

35 U.S.C. § 271(e)(1); *see Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 663 (1990) (interpreting § 271(e)(1) in the context of FDA regulations). A full appreciation of the FDA's approval process is therefore essential to a correct understanding of § 271(e)(1). The Federal Circuit, regrettably, all but ignored the mechanics of the FDA's approval process and as a result misconstrued the statutory safe harbor.

The process of scientific research and regulatory oversight leading to approval of a new drug[3] is lengthy and

[3] A "drug" subject to the FDA approval process is defined broadly. *See* 21 U.S.C. § 321(g)(1) (including within the definition any "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease").

complicated, and it does not always proceed in a straight line from original concept to marketable drug. The following description may not fully capture the complexity of the process, but provides background to guide proper interpretation of § 271(e)(1).

Typically, scientists begin the search for a new drug by identifying some medical problem they wish to solve. The researchers' ultimate therapeutic goal may be, for example, a treatment of a particular disease (such as Alzheimer's disease); an alternative therapy for a condition currently treated by an existing product (such as a new allergy drug); or a means of constraining the growth of a disease-causing agent (such as a protein that blocks certain cancer cells). At this earliest stage, however, scientists may have no idea what compound or compounds might achieve their goal. The research they conduct to identify candidate compounds, sometimes referred to as "drug discovery," can be quite broadly directed. *See infra* Part III (describing early-stage drug discovery techniques that fall outside the scope of § 271(e)(1)). Hundreds of candidates might show some promise, and additional research is then required to narrow the possibilities for further testing. A few of the candidate compounds identified by these experiments may come to market eventually as drugs approved by the FDA, but only after completion of lengthy drug development work and an elaborate regulatory process.

A new drug or "pioneer drug" typically must pass through two stages of regulatory approval. First, the FDA requires submission of an Investigational New Drug application ("IND"). 21 C.F.R. §§ 312.20(a), (b). An IND must report extensive data and evidence from *in vitro*[4] and

[4] *In vitro* studies occur in an artificial environment outside a living organism, as contrasted with *in vivo* studies, which are conducted on a live animal or human. *In vitro* studies may, for example, involve

animal studies – commonly referred to as "preclinical data" – in order to demonstrate that the candidate compound (or a group of closely related compounds) is safe enough to proceed to studies in humans. 21 C.F.R. §§ 312.22(a), (c). An applicant may conduct clinical investigations (defined as studies in human subjects, 21 C.F.R. § 312.3(b)) only after the FDA approves the IND. 21 C.F.R. § 312.20(b). The second stage, which occurs once the applicant has generated substantial evidence of safety and effectiveness based on "adequate and well-controlled studies" in humans, 21 C.F.R. § 314.126(b), is the submission of a New Drug Application ("NDA") which reports the clinical trial data and requests marketing approval. 21 C.F.R. § 314.50. The FDA cannot approve marketing of a compound as a treatment until the agency is satisfied of the compound's safety and effectiveness in treating a particular disease in humans. 21 U.S.C. §§ 355(a), (b)(1), (d).

FDA regulations spell out specific requirements for the content of the IND. *See* 21 C.F.R. § 312.23. The IND must include pharmacology and toxicology studies adequate to support the conclusion that the new drug is reasonably safe for initial human testing. 21 C.F.R. §§ 312.23(a)(5), (a)(8). The IND must also reflect any results from animal tests that suggest risks for humans such as carcinogenicity or teratogenicity (tendency to cause birth defects). 21 C.F.R. § 312.32(c)(1). The regulations also require "a section describing the pharmacological mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if

manipulation of cell cultures, cell membranes, or artificially created protein molecules. *In vitro* studies include safety profiling assays, in which a candidate compound is exposed to chemical receptors that occur naturally in humans in order to detect unwanted effects that the compound may induce in the body.

known" and "[a]n integrated summary of the toxicological effects of the drug in animals and *in vitro*." 21 C.F.R. §§ 312.23(a)(8)(i), (ii). In addition, an IND must provide information pertaining to the manufacture of the drug candidate. 21 C.F.R. § 312.23(7). Finally, the IND presents the proposed protocols for the clinical trials, subject to acceptance by the FDA. 21 C.F.R. § 312.23(a)(6) (proposed protocol included in IND); 21 C.F.R. § 312.20(b) (clinical studies may not begin until IND is in effect). After submission of the IND, an applicant must supplement it with any further information pertaining to the candidate drug's safety that comes to light as studies proceed. 21 C.F.R. § 312.23(a)(8).[5]

After the FDA approves the IND, the regulations provide for three phases of clinical investigation, which may overlap with one another as well as with continued animal or human studies of the new drug. 21 C.F.R. § 312.21.[6] The

[5] Although often the FDA is not involved in drug research prior to submission of an IND, the regulations provide that, for drugs intended to treat life-threatening or severely debilitating diseases, reviewing officials may meet with the applicant prior to submission of the IND "to review and reach agreement on the design of animal studies needed to initiate human testing." 21 C.F.R. § 312.83(a).

[6] In Phase 1, the initial introduction of the new drug into humans is undertaken. Phase 1 studies are typically performed in a small population, often of healthy subjects, and are aimed at establishing safety of the drug by determining its metabolic and pharmacological behavior in humans. 21 C.F.R. § 312.21(a). Phase 2 studies are conducted in relatively small populations of patients, and are focused on evaluating the effectiveness of the drug for a particular indication and identifying common short-term side effects. 21 C.F.R. § 312.21(b). Finally, once Phase 1 and 2 studies have provided preliminary evidence of the safety and efficacy of the drug, Phase 3 trials may begin. Phase 3 studies, which are often conducted in larger populations of up to thousands of patients, are directed toward evaluating the benefit of the drug against its risks and developing information necessary for proper labeling of the new drug. 21 C.F.R. § 312.21(c).

new drug's manufacturer submits the NDA to request marketing approval once sufficient data demonstrating the new drug's safety and effectiveness have been gathered from these human clinical studies and analyzed for statistical significance. The FDA will review the NDA before granting approval to market the new drug for a specified indication. The NDA is a comprehensive document which must include all information "pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source." 21 C.F.R. § 314.50. Thus, it includes the pharmacological and toxicological studies conducted *in vitro* and in animals as well as the results of all clinical studies. 21 C.F.R. § 314.50(d). In addition, an applicant may include in the NDA any studies that have been performed comparing either the effectiveness or the safety of the new drug to existing treatments, such as bioequivalence studies, epidemiological studies of side effects of similar drugs, or data on interactions between the new drug and other drugs. 21 C.F.R. §§ 314.50(3)(iii), (5)(vi).[7]

The procedure is much simpler and shorter when a manufacturer seeks FDA approval for a so-called "generic" drug, which generally has the same active ingredients as a drug already approved by the FDA. *See* 21 U.S.C. §§ 355(j)(2)(A), (C); 21 C.F.R. § 314.92. An applicant for

[7] The path from drug discovery through IND, clinical trials, NDA, and marketing approval is often iterative rather than linear. *See generally infra* Part II.B.1. The FDA may, and often does, provide feedback to the applicant at any stage of the process. *See, e.g.*, Michelle Meadows, *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA Consumer Mag., Jul.-Aug. 2002, http://www.fda.gov/fdac/features/2002/402_drug.html. After submission of the IND or NDA, the applicant may alter the drug's composition, the dosage or dosage form, the drug's manufacture, or the protocol for the clinical trials, and update the application to reflect these changes. *See* 21 C.F.R. §§ 314.70, 314.71 (providing procedures for updating applications).

approval of a generic drug may file an Abbreviated New Drug Application ("ANDA"). The ANDA applicant need only demonstrate that its product is "bioequivalent" to a drug previously approved (meaning that it operates in the body with the same effectiveness as the previously approved drug) and has similar "bioavailability" (the manner in which the drug is absorbed or becomes available at the site of physiological activity after administration). *See* 21 U.S.C. § 355(j)(2)(A)(iv). The ANDA may demonstrate bioequivalence or bioavailability by submitting data from *in vitro* studies or *in vivo* studies in humans. 21 C.F.R. § 320.24.[8] ANDAs "permit an applicant seeking approval of a generic drug to avoid the costly and time-consuming studies required for a pioneer drug." *Eli Lilly*, 496 U.S. at 676.

In sum, the FDA has issued a variety of testing requirements and guidelines for approval of drugs, which are by no means limited to testing in human clinical trials. Rather, in the process of approving clinical trials and ultimately marketing of a drug, the FDA will review a wide range of experimental data, including *in vitro*, animal, and human studies.

[8] Generic applicants may also submit a "paper NDA," which relies on previously published animal and human studies rather than on new preclinical and clinical data to satisfy the requirement of demonstrating safety and effectiveness. 21 U.S.C. § 355(b)(2); 21 C.F.R. § 320.22.

II. THE PANEL'S NARROW READING OF § 271(e)(1) IMPROPERLY EXCLUDES USES REASONABLY RELATED TO THE DEVELOPMENT AND SUBMISSION OF INFORMATION TO THE FDA.

Unlike previous courts examining the scope of § 271(e)(1), the Federal Circuit panel's decision makes little reference to the actual functioning of the FDA regulatory process described above. *Compare Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003) *with Eli Lilly*, 496 U.S. at 676-78. As a result, the decision inappropriately implies that the § 271(e)(1) safe harbor is narrow in two respects. First, the decision appears to suggest that the safe harbor is restricted to "clinical" experiments in human subjects. Second, the decision is open to the interpretation that the protection of § 271(e)(1) applies only to uses of a compound for which FDA approval eventually is sought. Both limitations distort the plain statutory text. The Federal Circuit panel's opinion needlessly departs from prior case law that was grounded in the statute and in the typical interactions between applicants and the FDA during the drug approval process. To correct these errors, this Court should order that the decision be vacated and remanded.

A. Limitation of the Safe Harbor to "Clinical" Experiments Would Ignore the Extensive Preclinical Data Required by the FDA.

The Federal Circuit panel's decision frames the question before it as "whether the *pre-clinical* research conducted under the Scripps-Merck agreement is exempt from liability ... under § 271(e)(1)." *Integra*, 331 F.3d at 865 (emphasis added). Elsewhere throughout its opinion, the panel repeatedly draws a distinction between clinical and pre-clinical research as if this difference were crucial to

defining the boundaries of the § 271(e)(1) safe harbor.[9] This language excludes all *in vitro* and animal studies from the safe harbor, because "clinical" studies in this context refer only to studies involving human subjects. *See* 21 C.F.R. § 312.3(b) (limiting the term "clinical investigations" to experiments with human subjects); Dorland's Illustrated Medical Dictionary 364 (29th ed. 2000) (defining "clinical" as "pertaining to or founded on actual observation and treatment of patients, as distinguished from theoretical or basic sciences").

Such an arbitrary dividing line ignores the fact that, as shown in the previous section, the FDA regulations contemplate submission of a wide range of *preclinical* data in both the IND and the NDA. These preclinical data include *in vitro* toxicology and pharmacology tests as well as animal studies. The use of the patented invention in conducting such preclinical studies falls squarely within the statute's protection "solely for uses reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1). There is simply no basis in the statutory text for limiting its reach to human trials, as the

[9] *See, e.g., id.* at 863 n.2 ("The issue before the jury was whether the infringing *pre-clinical* experiments are immunized from liability via the 'FDA exemption,' i.e., 35 U.S.C. § 271(e)(1).") (emphasis added); *id.* at 866 (paraphrasing the statute as sheltering uses "'reasonably related' to *clinical* tests for the FDA") (emphasis added); *id.* ("Scripps work sponsored by Merck was not *clinical* testing to supply information to the FDA . . . .") (emphasis added); *id.* at 867 (defining experiments as outside the safe harbor if they "form only a predicate for future FDA *clinical* tests") (emphasis added). While the Federal Circuit panel's opinion describes activities that are excluded from the safe harbor as early general research merely to identify potential drug candidates for FDA approval, its simple characterization of these activities as "pre-clinical" distorts the process of providing the FDA the information it requires.

language of the Federal Circuit panel's decision appears to do.

To draw this mistaken line between clinical and preclinical work, the panel relies heavily on legislative history in arguing that Congress' primary focus when it enacted the provision was on generic drugs. *Integra*, 371 F.3d at 866-67. In doing so, the panel errs for at least three reasons. First, using legislative history to contradict the plain meaning of statutory text is improper. *Rubin v. United States*, 449 U.S. 424, 430 (1981); *see Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1524 (Fed. Cir. 1992) (noting, in a case interpreting § 271(e)(1), that while legislative history may aid in understanding the statute, the court's duty is to enforce clearly-stated law as written). Second, even though generic drugs may have been the primary congressional focus, it is well established that § 271(e)(1) extends to all drugs and medical devices subject to FDA approval. *See Eli Lilly*, 496 U.S. at 679; *AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1029 (Fed. Cir. 1997).

Third, the actual functioning of the FDA regulations shows that, even following the panel's lead and gazing through the prism of generic drugs alone, preclinical work must be protected by § 271(e)(1). As the previous section explained, a generic drug manufacturer must demonstrate to the FDA the bioequivalence of the generic to a previously approved drug. *See* 21 U.S.C. § 355(j)(2)(A)(iv). The FDA regulations make clear that preclinical *in vitro* studies may provide the necessary evidence of bioequivalence. 21 C.F.R. § 320.24(a).[10] These *in vitro* studies should fall within the

[10] The House Report itself explicitly acknowledged that § 271(e)(1) covered "testing so that generic manufacturers can establish the bioequivalency of a generic substitute." H.R. Rep. No. 98-857, 98th Cong. 2d Sess., *reprinted in* 1984 U.S.C.C.A.N. 2647, 2692.

panel's own generic-centered formulation of the scope of § 271(e)(1). By limiting the exemption to human clinical studies, once again without regard to the statutory language or the FDA regulations, the Federal Circuit panel contradicts its own reasoning.

Because FDA regulations contemplate submission of extensive preclinical data in both the IND and the NDA, the Federal Circuit panel's apparent limitation of § 271(e)(1) to clinical research is erroneous.

B. The Federal Circuit Panel Improperly Limits the Safe Harbor to Testing of the Drug for Which Approval Ultimately Is Sought.

In its decision the Federal Circuit panel states that "[t]he FDA does not require information about drugs other than the compound featured in an Investigational New Drug application." *Integra*, 331 F.3d at 866. With this observation, the panel suggests that the § 271(e)(1) safe harbor protects only testing of a drug for which FDA approval ultimately is sought. The plain language of the statute, however, does not so limit the range of the exemption. Rather, the statute encompasses a wide range of activities involving other compounds that are nevertheless "solely for uses reasonably related to the development and submission of information" under FDA regulations. 35 U.S.C. § 271(e)(1).

1. A Candidate Drug May Change During Testing Aimed at FDA Approval.

Researchers frequently study a drug with the expectation of seeking FDA approval, but in response to ongoing testing they either change the drug or determine that

it is not suitable for its intended use. The infringement safe harbor under § 271(e)(1) must reach studies of these altered or abandoned compounds, even though the subject of such a study is not the exact compound for which approval is ultimately sought.

The FDA regulations contemplate that a drug may be altered in the course of safety and effectiveness studies. *E.g.*, 21 C.F.R. § 312.23(7) ("FDA recognizes that modifications to the . . . method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses."). For instance, the FDA regulations include procedures for updating or amending an IND or NDA after clinical studies are under way. 21 C.F.R. §§ 314.70, 314.71. These alterations may include the addition or deletion of an ingredient or other changes in the qualitative or quantitative composition of the drug. 21 C.F.R. § 314.70(b)(2). Thus, the regulations recognize that the compound on which early preclinical studies are performed may not be identical to the drug for which marketing approval is ultimately sought. In these circumstances, variants of the compound that were studied earlier must retain the protection of § 271(e)(1).

In addition to allowing changes, the regulations reflect the FDA's understanding that, at the time of filing an IND to seek approval for clinical studies, the applicant may not yet have determined the optimal drug candidate from a family of related drugs. The FDA thus allows applicants to file an IND seeking permission to conduct clinical studies on an entire family of related compounds, with the understanding that the applicant may not ultimately seek marketing approval for every compound studied. The FDA's Center for Drug Evaluation and Research ("CDER") encourages applicants intending to pursue such studies for a number of related compounds to submit a special IND, called a "screening IND," that covers "the review of multiple

active moieties or formulations" of a drug. *CDER Manual of Policies and Procedures, INDs: Screening INDs* 1 (2001), http://www.fda.gov/cder/mapp/6030-4.pdf. The purpose of the screening IND is to "compare the properties of closely related active moieties to screen for the *preferred* compounds or formulations." *Id.* at 2 (emphasis added). Under these regulations, an applicant submits data relating to multiple compounds, but both the applicant and the FDA acknowledge the likelihood that some of them will never be the subject of NDAs and will never be approved for marketing.

Finally, in the course of the multiple-stage process of seeking FDA approval for a drug, applicants often abandon some candidate compounds based on unfavorable test results. For example, an applicant might determine that Phase 3 clinical trials demonstrated unacceptable risks and terminate its research. It would be illogical for the scope of § 271(e)(1) protection to hinge on the favorable outcome of such experiments. The fact that the resulting data might never be reported to the FDA is irrelevant when applying § 271(e)(1). *See Nexell Therapeutics, Inc. v. AmCell Corp.*, 199 F. Supp. 2d 197, 204-05 & n.7 (D. Del. 2002) (noting that "if the defendant reasonably believes that . . . otherwise infringing activities would yield necessary information for FDA approval," activities are exempt even if the FDA subsequently disagrees); *Amgen, Inc. v. Hoechst Marion Roussell, Inc.*, 3 F. Supp. 2d 104, 109-10 (D. Mass. 1998) (noting that "[t]he exemption is not so ephemeral that it will be lost as a result of conduct which postdates the making, using, or selling of the patented product," such as abandoning studies); *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished opinion available at 1993 WL 87405) (noting that accused infringer should not "lose the exemption simply because it turns out, after the fact, that [a

study] either failed to generate information in which the FDA was interested or generated more information than [was] necessary to secure FDA approval").

There are many circumstances where studies which do not result in an IND or an NDA are nevertheless conducted as part of the overall FDA regulatory process and are therefore covered by the plain language of § 271(e)(1).[11] The Federal Circuit panel's narrow formulation of the statute here again reflects its failure to consider the full range of activities that can occur during the process of seeking FDA approval to market a drug.

2. Studies of Drugs Other Than the Drug For Which Approval Is Sought Are Often Pertinent to the FDA Review Process.

FDA regulations contemplate the submission of data comparing the drug for which approval is sought to other drugs and demonstrating the interactions of the drug for which approval is sought with other substances. Plainly, this critical data is "reasonably related" to the FDA regulatory process, but the Federal Circuit panel's narrow focus on only the drug for which an applicant seeks FDA approval may erroneously exclude it from the safe harbor.

For example, the FDA regulations governing NDAs contemplate the submission of bioequivalence and

[11] Legislative history indicates that Congress recognized, consistent with the text of § 271(e)(1), that the safe harbor would cover such studies. *See* H.R. Rep. No. 98-857, 98th Cong. 2d Sess., *reprinted in* 1984 U.S.C.C.A.N. 2647, 2678 (noting that a party deciding not to submit an application "is protected as long as the development [of information] was done to determine whether or not an application for approval would be sought").

bioavailability studies, which show that the drug for which approval is sought is metabolized by the body in a manner similar to a previously approved drug. *See* 21 C.F.R. § 314.50(c)(3)(iii); *see also* 21 U.S.C. § 355(j)(2)(A)(iv) (discussing submission of bioequivalence data for generic drugs in ANDA). Bioequivalence may be demonstrated through *in vivo* studies in humans or through *in vitro* studies that have been shown to be predictive of the drug's behavior in humans. 21 C.F.R. § 320.24. By the very nature of these requirements, the applicant will necessarily make use of the other compound that serves as the reference point for the comparison, and not only the drug for which approval is sought.

Similarly, the regulations require the submission of information concerning "potential adverse effects of the drug," 21 C.F.R. § 314.50(d)(5)(vi), as well as a description of "possible risks and side effects," 21 C.F.R. § 312.23(a)(5)(v). One method commonly used in the course of testing a drug to gather this required data is a "safety profiling assay" in which a candidate compound is exposed *in vitro* to substances normally found in the human body (such as chemical receptors) to detect any unwanted response that the candidate may stimulate. For example, an applicant seeking approval of a drug to treat ulcers may run *in vitro* studies that test the interaction of that drug with cloned neurotransmitter receptors, to ensure that the candidate drug does not interfere with normal brain function. At a minimum, these studies involve not only the drug for which approval is sought, but also the potentially infringing use of other substances, such as a cloned receptor.

Thus, when collecting data for the purpose of seeking approval of a particular drug candidate, the applicant may conduct bioequivalence or other comparative or safety studies that involve the use of a *different* substance for purposes "reasonably related to the development and

submission of information" to the FDA. These studies are a significant part of the FDA approval process for both new drugs and generic drugs, and therefore they must be protected under the statutory language of § 271(e)(1).

C. Decisions Prior to the Federal Circuit Panel Opinion Correctly Interpreted the Statute in Light of the FDA's Regulatory Process.

After Congress enacted the § 271(e)(1) exemption in 1984, courts endeavored to interpret and apply it in the context of the federal regulatory scheme governing the approval of drugs and medical devices. One district court decision, *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (unpublished opinion available at 1993 WL 87405), provided a thoughtful analysis that influenced many courts in determining the scope of the exemption. The *Intermedics* court stated the relevant question about the scope of the exemption as follows:

> Would it have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product?

Id. at 1280. The *Intermedics* court articulated this as a broad test, not a narrow one; it noted that the statutory language reflected a congressional "intention that the courts give parties some latitude in making judgments about the nature and extent of the otherwise infringing activities they would

engage in as they sought to develop information to satisfy the FDA." *Id.*

District courts have found the *Intermedics* test to be a useful approach to interpreting § 271(e)(1) in individual cases. As one court said in adopting the *Intermedics* test, activities fall within the § 271(e)(1) safe harbor if they "objectively bear reasonable prospects of yielding information that might be relevant in the FDA approval process." *Amgen*, 3 F. Supp. 2d at 108 (adopting *Intermedics* test as "consistent with the statutory scheme and existing Federal Circuit law"). Another court, quoting extensively from *Intermedics*, found promotional activities "conducted pursuant to soliciting clinicians to enter into FDA-approved clinical trials" protected by § 271(e)(1). *Nexell*, 199 F. Supp. 2d at 204-05 & n.7. A third court relied on the *Intermedics* test to find that production of a small number of commercial-scale batches of a product, for purposes of meeting the FDA's requirements that the defendant demonstrate its manufacturing capabilities, also was "reasonably related to the development and submission of information for the FDA." *NeoRx Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 205-07 (D.N.J. 1994). *See generally* 5 Donald S. Chisum, *Chisum on Patents*, § 16.03[1][d][iii] (1997 & 2004 Supp.) (discussing widespread influence of *Intermedics* on subsequent decisions interpreting § 271(e)(1)).

In the past, the Federal Circuit has also looked with favor upon the *Intermedics* standard. The original *Intermedics* decision itself was affirmed by the Federal Circuit without a published opinion. *See* 991 F.2d 808 (Fed. Cir. 1993). The Federal Circuit subsequently cited *Intermedics* with approval in *Telectronics*, where it found the safe harbor of § 271(e)(1) protected displays of a product at medical conferences for purposes of recruiting clinical investigators. *See* 982 F.2d at 1525 & n.5 (commending the

"carefully reasoned and exhaustive analysis" of the district court decision in *Intermedics*).

In the present case, the Federal Circuit panel purported again to employ the *Intermedics* test in its decision. *See Integra*, 331 F.3d 867. Yet the court went on to define § 271(e)(1) more narrowly than *Intermedics* or the many cases that followed it. By apparently limiting the safe harbor to clinical studies and to specific drugs for which FDA approval is ultimately sought, the panel opinion has needlessly departed from the developing consensus on the scope of § 271(e)(1).

III. THE § 271(e)(1) SAFE HARBOR DOES NOT EXTEND TO THE EARLIEST STAGES OF DRUG DISCOVERY.

Although the Federal Circuit panel's opinion interprets § 271(e)(1) too narrowly, it also expresses a legitimate concern that too broad a construction would be contrary to the statutory text and legislative intent. *Integra*, 331 F.3d at 867. The panel notes that § 271(e)(1) "simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." *Id.* Any such reading would disregard the statutory requirement that research within the safe harbor must be "solely for uses *reasonably related* to" the FDA approval process. 35 U.S.C. § 271(e)(1) (emphasis added).

The initial stages of drug research commonly focus on identifying compounds that show the potential for a therapeutic function from among thousands, or even tens of thousands, of possibilities. Such early-stage drug discovery efforts typically involve countless false starts and unsuccessful experiments for every promising compound identified for further study. Researchers often use techniques that require minimal advance hypothesis about

whether the numerous tested compounds will work as hoped, and that yield only random "hits" indicating which compounds merit further examination.

For example, biochemists have developed automated techniques, generally known as "high-throughput screening," to run multiple tests on large numbers of such compounds efficiently. These screening techniques often employ sophisticated research tools. *See* Donald R. Ware, *Research Tool Patents: Judicial Remedies*, 30 Am. Intell. Prop. L. Assn. Q.J. 267, 268 n.1, 269-70 (2002). "As it is now possible for a pharmaceutical company to screen several thousand molecules simultaneously in 30 to 50 different biochemical tests, the problem becomes one of feeding robots with interesting molecules." Camille G. Wermuth, *Strategies in the Search for New Lead Compounds or Original Working Hypotheses*, in The Practice Of Medicinal Chemistry 81, 86 (Camille G. Wermuth ed., 1996).

High-throughput screening techniques that involve little more than "feeding robots" should not be considered "reasonably related" to the development of information for the FDA. Their principal goal is the identification of candidates which may, at some later time after extensive further testing, be the subject of an IND or NDA application. The FDA is concerned with information *pertinent* to its consideration of safety or effectiveness. *See* 21 C.F.R. § 314.50. The reasons for the applicant's original identification of the compound or molecule for further study would be of little value in the FDA's analysis. Thus, high-throughput screening and similar techniques are unlikely to be "reasonably related to the development and submission of information" to the FDA as required in § 271(e)(1). Nor would they be covered by the *Intermedics* standard, because they do not "contribute (relatively directly) to the generation of the kinds of information that was likely to be relevant" to

the FDA. 775 F. Supp. at 1280. As such, these efforts should not be covered by the § 271(e)(1) safe harbor.

Petitioner here urged the Federal Circuit to adopt a broad and potentially unlimited construction of the safe harbor. According to petitioner's opening brief in that court, "Congress must have intended [§ 271(e)(1)] to encompass drug development research that serves *as a rational predicate to generating information for submission to the FDA*, including any tests conducted to determine whether to proceed with a drug candidate." Brief for Defendant-Appellant Merck KGaA (Feb. 13, 2002), at 45 (emphasis added). Petitioner's argument before this Court seems to retreat from this position without foreclosing it. *See, e.g.*, Pet. Br. at 28 (arguing that safe harbor protects "*any* experiment, so long as it would be reasonable for the researcher to believe the experiment could generate information of a sort the FDA considers at some point in its role as regulator of drugs") (emphasis added). Any standard akin to the "rational predicate" test argued before the Federal Circuit would sweep in virtually all early-stage drug discovery experiments. Such a standard would include basic scientific research far removed from the development of safety and effectiveness information considered by the FDA in its approval process.

The safe harbor provision is not an "elegant piece of statutory draftsmanship," *Eli Lilly*, 496 U.S. at 679, and Congress might be well advised to clarify its language in order to help researchers better understand where to draw the line. In any event, AIPLA urges this Court to confine its decision to correcting the Federal Circuit's erroneously narrow interpretation of the safe harbor, without reading the statute so broadly as to encompass all early-stage drug discovery research such as high-throughput screening.

Once this Court articulates the correct legal standard, the judgment of whether particular drug development experiments are "reasonably related" to the FDA approval process will be fact-specific. Pharmaceutical research techniques and the particular requirements of FDA regulations evolve continuously, and it will not be practical to define a fixed list of techniques and methodologies that fall within or outside the ambit of § 271(e)(1). It will be the province of the factfinder in individual cases to apply the general standard to these specific scenarios.

Remand in this case, therefore, is appropriate to determine whether the accused preclinical activities are entitled to the § 271(e)(1) safe harbor. AIPLA urges this Court to remand to the Federal Circuit for application of the correct legal standard to the facts in this case.[12]

IV. THE COMMON-LAW EXPERIMENTAL USE EXCEPTION HAS NO BEARING ON INTERPRETING § 271(e)(1) AND THE COURT SHOULD NOT ADDRESS IT.

The dissenting judge in the court of appeals believes that at least part of the allegedly infringing activity in this case is exempt from liability under the common-law experimental use exception, sometimes referred to as the "research exemption." *See Integra*, 331 F.3d at 874-76

[12] It is possible that some or all of the allegedly infringing uses made by Merck and Scripps constitute preclinical work reasonably related to generating information for the FDA to use in its regulatory process, and thus exempt from liability under § 271(e)(1). Petitioner so argues. *See* Pet. Br. at 43-50. The Federal Circuit should, however, consider that question under the deferential standard required to overturn a jury verdict on a motion for judgment as a matter of law. *See Union Oil Co. v. Atl. Richfield Co.*, 208 F.3d 989, 994 (Fed. Cir. 2000). AIPLA takes no position on the appropriate outcome of this process.

(Newman, J., dissenting). The dissent argues that "the statutory immunity of § 271(e)(1) takes effect wherever the research exemption ends." *Id.* at 876. This formulation misconstrues the experimental use exception, which applies in factual circumstances very different from those contemplated by the safe harbor under § 271(e)(1). The question presented by the petitioner does not implicate the scope of the common-law exception, and in any event the facts of this case do not raise the issue. AIPLA therefore urges this Court not to consider the scope and nuances of the common-law doctrine as part of its review.

The dissenting opinion in the Federal Circuit argues that it is appropriate to rely on the exception because it is "fundamental to resolution of the case." *Id.* at 878. The dissent views the experimental use exception and the § 271(e)(1) safe harbor as two segments of an unbroken continuum covering all experimental activity involving new drugs. *Id.* at 876. On the contrary, the facts of this case, and most scenarios involving the development of new drugs, fall well outside the experimental use exception as currently expounded by the Federal Circuit. Rather than segments of a continuum, these are two separate doctrines applicable to different types of activity.

The Federal Circuit has emphasized previously that the common-law experimental use exception is "very narrow and strictly limited." *Madey v. Duke Univ.*, 307 F.3d 1351, 1361 (Fed. Cir. 2002); *see Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1349 (Fed. Cir. 2000) (per curiam). The exception applies only to uses made "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry." *Madey*, 307 F.3d at 1362. If the ultimate purpose of research is commercial, then it cannot qualify for the experimental use exception. *Embrex*, 216 F.3d at 1349.

Here, Merck's intent to reap commercial benefits from drug discovery is unquestioned. Merck engaged Scripps scientists for the explicit purpose of commercializing a drug. More generally, research conducted to support FDA approval for marketing a drug, by its nature, seeks to further commercial ends and cannot qualify for the experimental use exception. Merck itself disavowed reliance on this defense before the Federal Circuit, and the issue was not briefed in that court. *Integra*, 331 F.3d at 863 n.2. The narrow focus of the experimental use exception on purely noncommercial activity simply does not apply to the facts presented here.

For these reasons, AIPLA urges this Court not to take up the issue in the present case. Neither the procedural posture nor the factual record provide any basis for judicial exposition on the common-law exception. The task of addressing any further exemptions from patent infringement arising in the course of basic research falls to Congress, not to this Court.

CONCLUSION

For the foregoing reasons, AIPLA urges the Court to vacate the Federal Circuit's decision and remand for further consideration of the facts of this case consistently with § 271(e)(1) and the entire FDA regulatory scheme for investigation and approval of new drugs.

Respectfully submitted,

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